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COVID-19 and pneumonia: a role for the uPA/uPAR system

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Research Highlights:

- The hCoVs induce inflammatory pneumonia, which in turn may cause ALI and ARDS
- The inflammatory process may be caused by dysregulated uPA/uPAR system
- Serum suPAR levels could represent a potential biomarker of disease progression
- Drugs targeting the uPA/uPAR system may be used for the treatment of hCoV infections

Here, we highlight recent findings on the urokinase plasminogen activator (uPA)/uPA receptor (uPAR) system that suggest its potential role as a main orchestrator of fatal progression to pulmonary, kidney, and heart failure in patients with coronavirus. Patients with prolonged background inflammation can present with aberrant inflammatory reactions, well recognized as the main factors that can result in death and probably sustained by a dysregulated uPA/uPAR system. SuPAR, the soluble form of uPAR, represents a biomarker of disease progression, and its levels correlate well with comorbidities associated with the death of patients with coronavirus. New drugs that regulate the uPA/uPAR system could help treat the severe complications of highly pathogenic human coronaviruses (hCoVs), including pandemic coronavirus 2019 (COVID-19).

Keywords: human coronaviruses; acute respiratory distress syndrome; biomarker; urokinase-type plasminogen activator receptor; formyl peptide receptors; UPARANT.

Teaser: A dysregulated uPA/uPAR system is present in several pathologies, including the comorbidities of patients with COVID-19. Thus, drugs regulating the uPA/uPAR system could reduce the mortality of pandemic COVID-19.

Introduction

Pandemic COVID-19 is of significant concern for the extended mortality, and impactful social and economic consequences worldwide. hCoVs include either low pathogenic strains that usually infect the upper respiratory tract. resulting in a mild, cold-like respiratory illness, or highly pathogenic strains, responsible for severe acute respiratory syndrome CoVs (SARS-CoV-1, and SARS-CoV-2, or COVID-19) and Middle East respiratory syndrome CoV (MERS-CoV), which mainly infect lower airways and can cause fatal progression [1–3].

SARS-CoV-2 is transmitted primarily through airways; on infection, the incubation period is ~4–5 days before symptom onset. When admitted to hospital, patients with COVID-19 typically exhibit fever and dry cough; less commonly, they show difficulty in breathing, muscle and/or joint pain, headache/dizziness, diarrhea, nausea, and the coughing up of blood. Severe COVID-19 cases progress to acute respiratory distress syndrome (ARDS), on average around 8–9 days after symptom onset [4]. Currently, no definitive cure for SARS-CoVs and MERS-CoV infections is available. Beside the use of antivirals, symptomatic and supportive treatment is a standard of care for patients with hCoV. The most commonly prescribed antiviral regimens in clinical settings are ribavirin, interferons and lopinavir, ritonavir, oseltamivir, chloroquine sulfate or hydroxy chloroquine sulfate [2,5]. A variety of other agents, including antiviral peptides, monoclonal antibodies, cell or viral protease inhibitors, have shown some effectiveness in *in vitro* and/or *in vivo* models [2]. Clinical trials of these other agents are awaited. Mycophenolic acid (MPA) is another

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potential therapeutic choice [5]. Frequently used as an immunosuppressive drug to prevent rejection in organ transplantation by inhibiting lymphocyte proliferation, MPA also prevents replication of viral RNA. However, MPA toxicity appears to exceed its potential benefits. Corticosteroids were extensively used during the SARS outbreak, generally in combination with ribavirin [2]. However, the use of corticosteroids in the treatment of hCoV-related diseases remains debated [6], and alternative anti-inflammatory drugs would be particularly useful, especially when ARDS occurs. Inhibitors targeting coronaviruses were recently reviewed elsewhere [7].

In this context, studies aiming to explore new approaches for both the early detection and treatment of coronavirus infections can have a significant impact in the fight against the disease.

Here, we highlight evidence that supports the potential role of uPA, its receptor uPAR, and the associated co-receptors (overall, the uPA/uPAR system) in the pathogenesis of hCoV-associated pneumonia and ARDS. The uPA/uPAR system might represent a new target for therapeutic interventions of the severe complications of hCoV infections, and the study of this system might provide an efficient biomarker of disease progression.

The disease caused by coronaviruses

The pathological and clinical course of the most severe lung injuries induced by hCoVs can be divided into three distinct phases. The early phase is characterized by robust virus replication associated with fever, cough, myalgia, and other systemic symptoms that generally improve in a few days. In the second phase, despite a progressive decline in virus titers, recurrence of fever, hypoxemia, and progression to pneumonia-like symptoms occur. During the late phase, ~20% of patients evolve to acute lung injury (ALI) and ARDS, which often results in death [8]. Given the progressive decline in virus titers, the late phase is thought to result from an overexuberant host inflammatory response [3].

Comorbidities are also important factors in the disease progression: chronic obstructive pulmonary disease (COPD), diabetes, hypertension, and malignancy were reported as main risk factors for reaching the composite endpoints in the Chinese-population during pandemic COVID-19 [9]. Similarly, hypertension, obesity, and diabetes were found to be the most common comorbidities for 5700 patients with COVID-19 in the New York City area [10]. All these comorbidities are sustained by a background prolonged inflammation.

Rapidly replicating pathogenic hCoVs can induce pneumonia with a mechanism that involves a massive inflammatory cell infiltration and elevated proinflammatory cytokine/chemokine production, which in turn can cause ALI and ARDS [3]. ARDS is a severe progressive form of lung injury occurring in patients who are critically ill, causing substantial morbidity and mortality [11]. It is characterized by diffuse alveolar injury, alveolar capillary leakage, neutrophil-derived inflammation, pulmonary edema formation, and surfactant dysfunction [12]. Clinical manifestations of ARDS include reduced lung compliance, bilateral pulmonary infiltrates, and severe hypoxemia [12]. Despite the latest advances in therapeutic intervention, ARDS represents a major cause of death in patients with SARS-CoVs or MERS-CoV worldwide [2,11].

In highly pathogenic hCoV infections, an exuberant inflammatory response correlates with the accumulation of inflammatory monocyte-macrophages, lymphocytes, and neutrophils into the alveolar wall and lumina of lungs, triggering an elevation of cytokine/chemokine levels, vascular leakage and impaired T cell activation [3,13,14]. Among the inflammatory mediators, tumor necrosis factor (TNF)-α, interleukins IL-1β, IL-6, IL-8, IL-10, granulocyte macrophage-colony stimulating factor (GM-CSF), intercellular adhesion molecule (ICAM)-1, substance P, chemokines, vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), keratinocyte growth factor (KGF), reactive oxygen species (ROS), and reactive nitrogen species (RNS) have been shown to have crucial roles in the pathogenesis of ARDS [15].

Beside immune cell infiltration and 'inflammatory storm', the pathophysiology of ARDS includes additional molecular mechanisms that lead to apoptosis of alveolar epithelial and capillary endothelial cells, and the development of fibrosis [16,17]. Apoptosis of epithelial and endothelial cells compromises the lung microvasculature and alveolar–epithelial cell barrier, causing vascular leakage and alveolar edema associated with tight junction (TJ) loss [18], ultimately resulting in hypoxemia [16]. By contrast, the accumulation of macrophages, fibroblasts, and myofibroblasts can lead to an abnormal deposition of collagen I and III, fibronectin, and other components of the extracellular matrix (ECM) in the alveolar compartment, thus altering the balance between profibrotic and antifibrotic mediators, and leading to a fibroproliferative response [17,19]. Evidence demonstrated that dysregulated angiogenic responses mediated by cytokines and growth factors, such as macrophage inflammatory protein-2, angiopoietin-2 and VEGF, may contribute to vascular lesions in ARDS and drive the fibroproliferative response [17,20]. Furthermore, in ARDS lung, damage to vascular endothelial cells promotes coagulation by activating platelets and procoagulant cascades, while reducing anticoagulant pathway and fibrinolysis, finally leading to the formation of microthrombi in the lung vasculature, and the deposition of fibrin in intra-alveolar and interstitial compartment. The procoagulant activity is promoted by inflammatory mediators during the early stages of ARDS. Water channel aquaporins also have an important role in ARDS, facilitating water permeability between the alveolar compartment and vasculature. Up- or downregulation of various aquaporins have been investigated in induced ARDS animal models [21].

The physiological and pathological role of the uPA/uPAR system

uPAR (CD87) is a receptor comprising three domains (D-I, D-II and D-III) anchored by glycosylphosphatidylinositol (GPI) to the surface of various cell types, including immune cells, especially neutrophils, monocytes, and macrophages [22]. uPAR binds uPA, and transforms plasminogen into plasmin, which in turn initiates a series of proteolytic

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cascades to degrade the components of the ECM. This process traces the path of immune cell migration towards a chemotactic gradient. Migrating cells undergo profound cytoskeletal rearrangements required for cell movement. Leading-edge detachment, cytoskeletal rearrangement, and attachment occur cyclically during cell migration. uPAR orchestrates this function. Upon uPA binding, uPAR changes its conformation and exposes the chemotactic sequence Ser^{88}-Tyr^{92}. Given its lack of a transmembrane domain, GPI-anchored uPAR has high mobility on the cell surface and can interact with later partners with the ability to communicate with the internal cell compartment to produce downstream intracellular signaling mediated by effector molecules, such as the focal adhesion kinase, Src, and Akt. uPAR binds vitronectin, and multiple cell receptors, such as different types of transmembrane receptor [the formyl peptide receptors (FPRs), integrins, and VEGFR2 [23]], establishing crosstalk between membrane-bound uPAR and its co-receptors.

FPRs are a family of three human receptors (FPR1, FPR2, and FPR3). FPR1 was first identified to bind bacterial formyl-methionyl-leucyl-phenylalanine (fMLF). FPRs are essential for host defense against the invasion of pathogens, malignancies, and expansion of traumas, whereas abnormal expression of FPR function can be harmful [24]. FPRs are also subject to homologous and heterologous desensitization (of other chemoattractant G-protein-coupled receptors): excessive activation of the receptor by a ligand causes the unresponsiveness of the receptors to subsequent stimulation by the same or other ligands. Therefore desensitization of immune-competent cells could be detrimental for host defense [25]. Human mitochondrial formylated peptides derived from cell death activate FPR1 signaling, and are recognized as key drivers of ALI/ARDS [26]. FPR1 inhibitors (such as cyclosporin H) preserve normal neutrophil bacterial phagocytosis or superoxide production in response to infections. Therefore, mitigating FPR1 homologous and heterologous desensitization can protect the host from systemic sterile inflammation and secondary infection following tissue injury or primary infection [27].

Crosstalk between membrane-bound uPAR and FPR1 [28] is particularly important, and a dysregulated uPA/uPAR system has profound effects on cell response to exogenous stimuli. uPAR interacts functionally with FPR1 through the Ser^{88}-Tyr^{92} sequence located at the hinge connecting the D-I and D-II domains. Physiological proteolysis of uPAR generates cell-surface truncated forms lacking the N-terminal D-I. Cleaved uPAR does not bind uPA and vitronectin, and does not co-immunoprecipitate with integrins, but it still contains and exposes the chemotactic Ser^{88}-Tyr^{92} sequence, resulting in the retention of its ability to functionally interact with FPRs [26]

Soluble uPAR peptides, bearing the Ser^{88}-Tyr^{92} sequence, are also ligands for FPRs and induce migration of various cell types [29]. Ser^{88}-Tyr^{92}-dependent signaling is supported by crosstalk between the high-affinity FPRs and the α_v chain of integrins [29]. SuPAR is obtained upon cleavage of the GPI anchor. This form regulates the activity of inflammatory chemokine receptors, such as MCP-1 and RANTES receptors, through FPR activation [30]. The activity of the uPA/uPAR system is mainly modulated by the plasminogen activator-inhibitor 1 (PAI-1), which belongs to the serine protease inhibitors (SERPIN) family. Interaction of PAI-1 with uPA diminishes the binding affinity of the latter to vitronectin [31]. Furthermore, PAI-1 induces the internalization and degradation of uPAR-bound uPA through the cooperation of low-density lipoprotein receptor (LDLR)-like proteins [32]. Given its role in preventing plasmin formation, PAI-1 acts as the main inhibitor of fibrinolysis. Not unexpected, significantly high PAI-1 levels have been detected in patients with SARS-CoV who have developed ARDS, because they are associated with a severe hypofibrinolytic state [33].

Target identification

The uPA/uPAR system is reported to be dysregulated in several pathologies: cancer, pulmonary fibrosis, kidney disease, coronary artery disease, rheumatoid arthritis, systemic sclerosis, bone destructive disease, lupus erythematosus, Alzheimer's disease, psoriasis, and endometriosis (see refs in [34]). These pathologies well match the comorbidities of COVID-19.

During the late-phase clinical course of highly pathogenic hCoV, comorbidities are important factors in the development of disease complications that often result in death. Only in few cases have no comorbidities been reported. The most common comorbidities reported for COVID-19 are COPD, diabetes, hypertension, and malignancies, all characterized by a background prolonged inflammation. An upregulated uPA/uPAR system is related to: (i) elevated levels of proinflammatory cytokines/chemokines; ii) epithelial and endothelial cell proliferation and impaired tissue remodeling; (iii) epithelial and endothelial cell apoptosis; (iv) loss of adequate TJ-mediated cell–cell contact; (v) aquaporins dysregulation; (vi) VEGF-dependent compromised microvasculature; and (vii) hypoxia.

uPAR interacts with cell membrane receptors, such as integrins, FPRs, and VEGFR2. FPR1 is at the forefront in terms of recognizing formyl-peptides released both from bacteria and death host cell digested proteins. A war against the cause of tissue damage begins. FPR1 immediately communicates with uPAR, and a multitude of functions to defeat the invader and to repair the injured tissues under attack begin. Beside the proteolytic function of uPAR on uPA, essential for tissue remodeling and immune cell migration/activation, corresponding to a recall of reinforcements from the rear, uPAR back communicates to the cells that the counterattack was launched, to equilibrate proinflammatory/anti-inflammatory signals, avoiding damage from friendly fire, and to upregulate repair functions. In many cases, the repair process completely recovers tissue and organ function. In some cases, the back communication fails, and proinflammatory signals prevail, causing an aberrant immune response. uPAR is well recognized as the main orchestrator of monocyte-macrophage and neutrophil accumulation in injured tissue. An excessive concentration of signal molecules can desensitize FPRs, and communication with uPAR might be

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interrupted. Whether this desensitization causes a robust virus titer and expansion remains to be proven. However, FPRs antagonists might abrogate desensitization.

Diagnostic value of the uPA/uPAR system

SuPAR is present in the serum, but it can also be found in the cerebrospinal fluid, urine, saliva, or pleural, peritoneal, and pericardial fluids [35]. To date, most research has focused on suPAR levels in the serum. SuPAR levels can easily be determined [36], at a relatively low cost, by the use of a commercially available ELISA or by turbidimetric immunoassays [37]. In addition, suPAR levels are stable in stored plasma and serum samples, and their quantification is reproducible in samples that have been stored for >5 years at –80°C despite exposure to multiple freeze–thaw cycles [38]. SuPAR has been proposed as a biomarker of immune system activation, and its use is being revised in a variety of diseases, as summarized in Table 1 [39–53].

Quantification of suPAR levels has also been proposed for the assessment of severity in several pathologies, including pneumococcal pneumonia [54], children with pneumonia [55], and idiopathic pulmonary fibrosis (IPF) [56]. It also predicts the elevated risk of ARDS in patients with sepsis and is positively associated with inflammation and mortality [57]. Importantly, suPAR reflects the level of the immune system activation, regardless of its etiology (viral, bacterial, parasitic, or other). Figure 1 compares the suPAR levels in healthy controls and patients and enables the defining of a cut-off limit of 4 ng/ml of suPAR to alert for the prognosis of severe complications.

SuPAR levels during hCoV infections have been very recently determined for the first time, revealing even in this case, an activation of the immune system [58].

Evaluation of suPAR levels in stored samples of SARS-CoV-1 and MERS-CoV could widen the statistical analysis. However, this preliminary study confirms the need to determine the suPAR levels in serum of patients with hCoV to provide important indications for required early admission and treatment in ICU.

Target validation

There is a growing number of drugs under development acting as: (i) broad-spectrum antiviral agents; (ii) viral enzyme inhibitors; (iii) interferons; (iv) immunomodulators; (v) corticosteroids; and (vi) vaccines. Immunomodulators involving the uPA/uPAR system have been described, and a selection is reported in Table 2 [59–71]. However, therapies capable of restoring to normality a dysregulated uPA/uPAR system are not yet available, although they could be particularly beneficial in reducing ICU admission, and in ARDS therapy.

Several peptide-based compounds have been found to interfere with a dysregulated uPA/uPAR system in *in vivo* models of several pathologies of different etiology. Some of these compounds have been designed from the chemotactic Ser^{88}-Tyr^{92} sequence of uPAR, based on the finding that even subtle modifications of this sequence can significantly alter uPAR-mediated recognition processes [72]. Peptides, including pyroGlu-Arg-Glu-Arg-Tyr-NH_2 (pERERY-NH_2) [62], Ac-Arg-Glu-Arg-Phe-NH_2 (RERF) [63], Ac-Arg-Aib-Arg-α(Me)Phe-NH_2 (UPARANT) [64], cyclic head-to-tail Ser-Arg-Ser-Arg-Tyr (c[SRSRY]) [65], Ac-D-Tyr-D-Arg-Aib-D-Arg-NH_2 (RI-3) [66], and Ser-Arg-Ser(P)-Arg-Tyr-NH_2 (SRS(P)RY) [67], were demonstrated to share the same binding site with $uPAR^{88-92}$, thus competing with the latter for binding to transmembrane receptors. As one of the most illustrative examples, UPARANT (cenupatide) interferes, independently from uPA activation, with FPRs and integrins, preventing agonist-dependent FPR internalization in endothelial cells, even at nM concentrations. While originally proposed as an antimetastatic agent, UPARANT was then explored as anti-inflammatory drug and to treat diabetes complications and ocular pathologies [34]. In CD-1 mice and Wistar rats, intraperitoneal administration of UPARANT at 12–24 mg/kg reduced inducible nitric oxide synthase (iNOS), cyclo-oxygenase 2 (COX2), and nitric oxide (NO) overproduction subsequent to carrageenan-induced paw edema, and zymosan-induced peritonitis [73]. In genetically modified fatty rats (Torii rats) [74], subcutaneous administration of UPARANT at 7 mg/kg (three times a week) prevented the onset of diabetes retinal complications by reducing vascular leakage into the eye. UPARANT administration prevented the dysregulation of blood–retinal barrier markers (BRB), downregulating the levels of transcripts and proteins of BRB markers, including the transmembrane components of the interendothelial TJs, claudin-1, claudin-5, and zonula occludens-1. In streptozotocin-induced diabetic nephropathy in Sprague–Dawley rats [75], subcutaneous administration of UPARANT at 8 mg/kg for 5 days restored vascular permeability integrity, and increased aquaporin-2 expression in the medulla. In animal model of retinitis pigmentosa [76], 16 mg/kg via subcutaneous injection of UPARANT at postnatal day 10 and continued daily until postnatal day 30 significantly reduced the Bax:Bcl2 ratio and active caspase-3 levels, limiting apoptosis, but autophagy.

Drugs targeting the dysregulated uPA/uPAR system might represent candidates for the treatment of severe lung injury resulting from hCoV infections or of other different etiology.

It was demonstrated that UPARANT is a strong anti-inflammatory drug in animal models, acting with a mechanism different from corticosteroids and nonsteroidal anti-inflammatory drugs [34]. UPARANT has the following characteristics that well match with counteracting the pathological signs of ARDS: (i) reduces inflammatory cell infiltration; (ii) reduces proinflammatory cytokines/chemokines; (iii) abrogates vascular leakage; (iv) significantly reduces edema; (v) inhibits monocyte-macrophage and neutrophil accumulation; (vi) reduces endothelial cell apoptosis; (vii) restores blood barrier integrity, limiting fluid extravasation; (viii) ameliorates hypoxia-induced reaction cascade; and (ix) blocks impaired tissue remodeling.

Concluding remarks

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The evidences that mortality in COVID-19 is related to the presence of various comorbidities brought us to investigate the possibility of identifying a key biological process related to these comorbidities.

First, literature data suggested that suPAR levels in serum of patients with different pathologies are elevated (>4 ng/ml), with good statistical significance, when compared with healthy controls. Among these pathologies, there are many corresponding to comorbidities of patients with hCoV. Therefore, with this review, we are inviting clinical biochemists to study suPAR levels in patients with hCoV.

Second, we observed from literature data that elevated suPAR levels in serum are also representative of background prolonged inflammation. In turn, elevated suPAR levels and prolonged background inflammation mirror a dysregulated uPA/uPAR system. Therefore, we propose the uPA/uPAR system as a therapeutic target to reduce mortality of COVID-19.

Finally, we highlight the uPA/uPAR system as potential target that has been validated in animal models by the use of UPARANT. UPARANT is classified as an anti-inflammatory molecule, acting with a mechanism different from corticosteroid and nonsteroidal anti-inflammatory drugs. UPARANT has been shown to be effective in various disease models independently from their etiology. However, clinical evidence is awaited.

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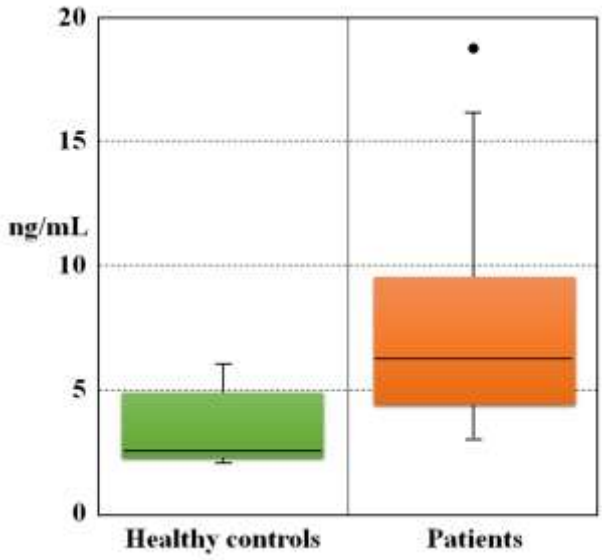

Figure 1. Box plot describing soluble urokinase plasminogen activator (suPAR) levels in healthy controls and patients, as in detailed in Table 1 in the main text.

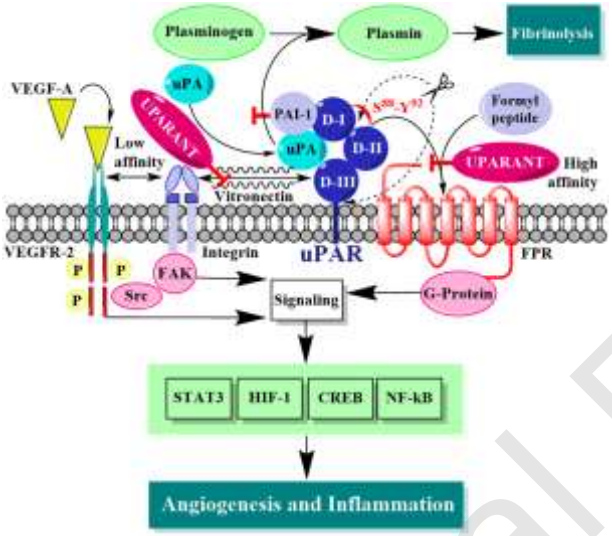

Figure 2. Hypothetical model of urokinase plasminogen activator (uPA)/uPA receptor (uPAR) system function. Upon binding to uPAR, uPA catalyzes the conversion of plasminogen into plasmin, a serine protease involved in extracellular matrix (ECM) degradation and cell motility. Plasminogen activator-inhibitor 1 (PAI-1) is a negative regulator of the plasminergic system [77]. Upon uPA binding to uPAR, a conformational transition occurs, and the uPAR^{88,92} sequence is exposed and can participate in binding with lateral co-receptors. In addition, chymotrypsin and cathepsin G hydrolyze uPAR at the D-I:D-II linker region, giving rise to a truncated D-II D-III GPI-anchored uPAR and to the peptide fragment S^{88}RSRY^{92}. Furthermore, uPAR can be detached from the GPI anchor, leading to the full or truncated soluble (su)PAR form. Beside its upstream role in fibrinolysis, uPAR lacking an intracellular domain forms supramolecular complexes by interacting with transmembrane receptors: formyl peptide receptors (FPRs), integrins (mainly, αvβ3 integrin), and vascular endothelial growth factor receptor 2 (VEGFR-2). FPR can also be activated by the peptide fragment S^{88}RSRY^{92}, and formylated mitochondrial or bacterial peptides. VEGFR-2 can also be activated by VEGF-A. The activation of these co-receptors subsequently produces intracellular signaling that ends with the synthesis of proangiogenesis and proinflammatory mediators. The uPA/uPAR system is also represented on the cell surface [34,76,78]. UPARANT binds with very high affinity to FPR1 and with lower affinity to αvβ3 integrin, and antagonizes uPAR co-receptor activation, affecting the plasminergic system and fibrinolysis. Abbreviations: CREB, cAMP response element-binding protein; FAK, focal adhesion kinase; HIF-1, hypoxia inducible factor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Src, proto-oncogene tyrosine-protein kinase; STAT-3, signal transducer and activator of transcription 3.

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Table 1. SuPAR levels (ng/mL) in serum, or otherwise specified, of healthy controls and patients[a]

Pathology	suPAR levels (ng/ml)		Refs
	Healthy controls	Patients	
Diabetic nephropathy (DN)	2.3±0.5	4.4±1.6	[39]
Severe acute pancreatitis (SAP)	5.2 (2.0–8.0)	16.1 (12.6–24.2)	[40]
Moderate-severe acute pancreatitis (MSAP)	5.2 (2.0–8.0)	12.2 (9.6–17.0)	[40]
Moderate acute pancreatitis (MAP)	5.2 (2.0–8.0)	9.4 (6.9–12.0)	[40]
Asthma	2.5 (1.9–3.3)	5.6 (3.6–7.7)[b]	[41]
Systemic lupus erythematosus (SLE)	3.2 (2.9–3.0)	4.5 (3.8–5.2)[c]	[42]
Cirrhosis	2.6 (1.3–7.8)	7.2 (1–27.4)[d]; 6.8 (1–29.4)[e]	[43]
Critical Illness	2.1 (0.0–3.5)	5.9 (2.1–24.1)[f]; 9.7 (0.4–38.0)[g]; 8.3 (1.5–38.0)[h]; 10.8 (0.4–38.0)[i]	[44]
Cardiovascular disease (CVD)[i]	3.9 (3.3–4.7)	4.55 (3.8–5.5)[b]	[45]
Ventilator-associated pneumonia (VAP)[j]	4.7 (3.6–6.3)	6.6 (5.7–7.7)	[46]
Community-acquired pneumonia[j]	2.7±1.4	4.0 ±2.3	[47]
Acute exacerbation COPD)	2.4±0.9	4.8±1.9	[48]
Diabetes type 2	2.1 (1.9–2.4)	3.0 (2.5–3.5)	[49]
Diabetes type 1[j]	2.3 (1.1–3.6)	3.0 (1.1–10.5)[l]; 3.6 (1.6–15.1)[m]; 4.9 (1.8–13.2)[n]	[50]
Cigarette smoke[k]	2.1±0.1	3.3 ±0.2	[51]
Sepsis[k]	6.0 (3.7–10.8)	18.8 (6.8–30.1)	[52]
Bacteremia in patients with systemic inflammatory response syndrome	5.65 (4.30–7.83)	8.1 (5.8–15.5)[o]; 9.6 (6.5–11.7)[p]	[53]

[a]Median values [n ± SD, n (range, 95% CI) or n (IQR)] of serum suPAR levels, unless otherwise stated.

[b]Died.

[c]Estimated glomerular filtration rate <90 ml/min/1.73 m^2.

[d]Hepatic vein.

[e]Femoral artery.

[f]Standard-care patients with bacterial infections (SC).

[g]ICU patients

[h]Patients in ICU without sepsis.

[i]Patients in ICU with sepsis.

[j]Plasma suPAR levels.

[k]suPAR levels from blood samples.

[l]Normoalbuminuria.

[m]Microalbuminuria.

[n]Macroalbuminuria.

[o]Gram-positive bacteremia.

[p]Gram-negative bacteremia.

Table 2. Selected immunomodulators involving the uPA/uPAR system

Compound	Receptor	Refs
Boc-MLF (BOC1)	FPR1/FPR2	[59]
Boc-FLFLFL (L-BOC2)	FPR1/FPR2	[59]
D-BOC2	FPR3	[60]
Cyclosporins H and A	FPR1	[59]
WRW4	FPR2/FPR3	[61]
PBP10	FPR2	[61]
pERERY-NH_2	FPR1	[62]
RERF	FPR1	[63]
UPARANT	FPR1	[64]
c[SRSRY]	FPR1	[65]
RI-3	FPR1	[66]
SRS(P)RY	FPR1	[67]
CHIPS	FPR1	[59]
CDCA	FPR1/FPR2	[68]
DCA	FPR1	[68]
3570-0208	FPR1	[68]

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10-(6-hexyl-2-methyl-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-7-yl acetate)	FPR1	[69]
4-Aroyl-3-hydroxy-5-phenyl-1H-pyrrol-2(5H)-ones	FPR1	[70]
BVT173187	FPR1	[71]

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